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(54) Title: ASSAYS RELATING TO TOLL-LIKE RECEPTOR ACTIVITY

(57) Abstract: The present invention provides assays useful for detecting agonists of Toll-like receptors. The assays include providing a cell culture transfected with a nucleic acid sequence that encodes a reporter operably linked to a TLR-inducible expression control sequence.

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## ASSAYS RELATING TO TOLL-LIKE RECEPTOR ACTIVITY

### Background of the Invention

Cells of the immune system secrete a diverse set of compounds including  
5 cytokines, chemokines, co-stimulatory markers, and defensins in response to an immunological challenge.

Certain compounds known as immune response modifiers ("IRMs") possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs effect their immunostimulatory activity by, e.g., inducing the production and  
10 secretion of certain cytokines while inhibiting production and secretion of other cytokines. Certain IRMs are small organic molecules such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,482,936; 5,494,916; 6,110,929; 6,194,425; 4,988,815; 5,175,296; 5,367,076; 5,395,937; 5,693,811; 5,741,908; 5,238,944; 5,939,090; 6,245,776; 6,039,969; 6,083,969; 6,245,776; 6,331,539;  
15 and 6,376,669; and PCT Publications WO 00/76505; WO 00/76518; WO 02/46188, WO 02/46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; and WO 02/46194.

Additional small molecule IRMs include purine derivatives (such as those described in U.S. Patent Nos. 6,376,50 and 6,028,076), small heterocyclic compounds  
20 (such as those described in U.S. Patent No. 6,329,381), and amide derivatives (such as those described in U.S. Patent No. 6,069,149).

Other IRMs include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,1994,388; 6,207,646; 6,239,116;  
25 6,339,068; and 6,406,705. Other IRM nucleotide sequences lack CpG and are described, for example, in International Patent Publication No. WO 00/75304.

Some of these IRMs induce cellular responses (e.g., the production and/or secretion of cytokines, chemokines, etc.) through one or more Toll-like receptors (TLRs). For example, certain small organic molecule IRMs are agonists of one or more of TLR-1,  
30 TLR-2, TLR-4, TLR-6, TLR-7, and TLR-8. Additionally, CpG has been reported to act through TLR 9.

In certain cells of the immune system, TLR activation can be associated with activation of the transcription factor NF- $\kappa$ B. NF- $\kappa$ B activation is associated with certain cellular responses to an immunological challenge, such as the production and secretion of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. IRM induction of such cellular responses can be demonstrated by measuring activation of the transcription factor NF- $\kappa$ B in response to exposing a cell to an IRM compound (See, e.g., Chuang *et al.*, *Journ. of Leuk. Biol.*, vol. 71, pp. 538-544 (2002), and Hemmi *et al.*, *Nature Immunology*, vol. 3(2), pp. 196-200 (2002)). Thus, NF- $\kappa$ B activation can be used as a reporter of TLR activation. However, the extent of NF- $\kappa$ B activation does not necessarily correlate with the extent of the downstream cellular response. This is so because the downstream cellular response may be modulated by one or more additional factors.

#### Summary of the Invention

The present invention provides assays for detecting activation of a TLR. The assays include providing a cell culture comprising cells transfected with a nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to an expression control sequence that is induced by activation of a TLR and comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter; exposing the cell culture to a compound that activates a TLR; providing conditions effective for generating the detectable signal; and detecting the detectable signal.

In another aspect, the present invention provides assays for identifying agonists of a TLR. The assays include providing a cell culture comprising cells transfected with a first nucleic acid sequence that comprises a nucleotide sequence that encodes a TLR operably linked to a first expression control sequence, and a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that is induced by activation of a TLR; contacting the cell culture with a test compound; providing conditions effective for generating the detectable signal, thereby generating a TLR-

mediated detectable signal; and identifying the compound as an agonist of the TLR if a TLR-mediated detectable signal is detected.

5 In another aspect, the present invention provides assays for identifying antagonists of a TLR. These assays include providing a cell culture that comprises cells transfected with a first nucleic acid sequence that comprises a nucleotide sequence that encodes the TLR operably linked to a first expression control sequence, and a second nucleic acid sequence that encodes a reporter that (a) is operably linked to a second expression control sequence that is induced by activation of a TLR, and (b) generates a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective  
10 for generating the detectable signal; contacting the cell culture with an agonist of the TLR and a test compound; providing conditions effective for generating the detectable signal, thereby permitting the cell culture to generate a full TLR-mediated detectable signal in the absence of an antagonist of the TLR; measuring the detectable signal; and identifying the compound as an antagonist of the TLR if the detectable signal is less than a full TLR-mediated detectable signal.  
15

In another aspect, the present invention provides a TLR agonists and TLR antagonists identified using an assay according to certain embodiments of the present invention.

20 In yet another aspect, the present invention provides pharmaceutical compositions including a TLR agonist or a TLR antagonist identified using an assay according to certain embodiments of the present invention.

Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, and claims. In several places throughout the specification, guidance is provided through lists of  
25 examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

#### **Detailed Description of Illustrative Embodiments of the Invention**

30 The present invention provides assays that may be useful for detecting TLR activation based on detecting induction of a downstream cellular response to TLR activation (e.g., production or secretion of one or more immune system compounds such as cytokines or co-stimulatory markers) rather than NF- $\kappa$ B activation. In some cases, the

cellular response may be mediated by NF- $\kappa$ B, but in other cases the cellular response may be NF- $\kappa$ B-independent. Thus, the present invention provides assays that may be useful for detecting a broader range of TLR activation than is possible by monitoring NF- $\kappa$ B activation. This may provide an ability to identify certain TLR agonists that would not be  
5 detected using an assay based on NF- $\kappa$ B activation. The assays of the present invention also may provide a more relevant indication of the quantitative character of a particular cellular response to TLR activation by a particular TLR agonist.

In some cases, an assay according to the present invention may be useful for detecting TLR activation that is not accompanied by NF- $\kappa$ B activation. Such an assay  
10 may be employed to identify TLR agonists that do not necessarily also activate NF- $\kappa$ B. Such TLR agonists may be useful for treatment or prevention of certain conditions in which the production and secretion of pro-inflammatory cytokines such as those induced by NF- $\kappa$ B activation may be undesirable.

For purposes of this invention, the following terms shall have the meanings set  
15 forth.

“Activation” refers to modifying the indicated protein so that the protein provides a biological function. For example, TLR activation refers to modifying a TLR, such as in response to exposure of the TLR to an agonist, so that the TLR is capable of inducing the production and secretion of certain cytokines.

20 “Agonist” refers to a compound that can combine with a receptor (e.g., a TLR) to produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results in the modification of another compound so that the other compound directly binds to the  
25 receptor. An agonist may be referred to as an agonist of a particular TLR (e.g., a TLR6 agonist).

“Amino acid sequence” refers to a particular ordered sequence of amino acids, whether naturally occurring or engineered.

30 “Antagonist” refers to a compound that can combine with a receptor (e.g., a TLR) to inhibit a cellular response. An antagonist may be a ligand that directly binds to the receptor. Alternatively, an antagonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b)

otherwise results in the modification of another compound so that the other compound directly binds to the receptor. An antagonist may be referred to as an antagonist of a particular TLR (e.g., a TLR6 antagonist). An antagonist may inhibit biological activity to any measurable extent.

5           “Co-transfect” and variations thereof refer to transfecting a host cell with more than one vector. A host cell may be co-transfected by transfecting with two or more vectors one at a time or in any convenient combination of vectors, including simultaneous transfection with all vectors.

          “Express/expression” refers to the ability of a cell to transcribe a structural gene to  
10       mRNA, then translate the mRNA to synthesize a protein that provides a detectable biological or biochemical function. “Expressible” refers to the ability of a particular nucleic acid sequence to be expressed by a cell that contains the nucleic acid sequence.

          “Immune system compound” refers to any compound that is produced or secreted by cells of the immune system in response to an immunological challenge. Immune  
15       system compounds include but are not limited to cytokines, chemokines, co-stimulatory markers, and defensins.

          “Inhibit” refers to any measurable reduction of biological activity.

          “IRM compound” refers to a compound that alters the level of one or more immune system compounds when administered to an IRM-responsive cell. Representative  
20       IRM compounds include the small organic molecules, purine derivatives, small heterocyclic compounds, amide derivatives, and oligonucleotide sequences described above.

          “Nucleic acid sequence” refers generally to a region of DNA that has a definable function such as (a) encoding a peptide, polypeptide, or protein or (b) controlling  
25       expression of a nucleic acid sequence that encodes a peptide, polypeptide, or protein. For example, a nucleic acid sequence that encodes TLR6 refers generically to any sequence of nucleotides that encodes a TLR6 protein, without regard to (a) the species source of the nucleic acid sequence, (b) specific nucleotide sequence variants, or (c) whether such nucleotide sequence variants are naturally occurring or engineered.

30       “Nucleotide sequence” refers to a particular ordered sequence of nucleotide bases, whether naturally occurring or engineered.

“TLR-mediated detectable signal” refers to a detectable signal or that portion of a detectable signal that is attributable to activation of a TLR expressed from a gene expression system transfected into a host cell. For example, a host cell may naturally generate a background level detectable signal ( $S_0$ ), but generate a greater detectable signal ( $S_T$ ) after being transfected with, and then expressing, a nucleic acid sequence that encodes a TLR. Thus, the TLR-mediated detectable signal ( $S_{TLR}$ ) refers to the portion of the detectable signal generated by the transfected cell that is greater than background:  $S_{TLR} = S_T - S_0$ .

It has been found that induction of certain secreted proteins or polypeptides can be useful as reporters of TLR activation. For example, IFN- $\alpha$  is a cytokine secreted by such immune system cells as T lymphocytes, macrophages, plasmacytoid monocytes, dendritic cells, and natural killer cells. IFN- $\alpha$  is involved in regulating a host's innate and adaptive immune responses to an immunological challenge, perhaps by providing a link between the two responses [Brassard *et al.*, *Journal of Leukocyte Biology* 71: 565-581 (2002)]. The innate immune response can include the cell-mediated response of natural killer (NK) cells to a non-self (e.g., neoplastic) or foreign (e.g., viral) antigen. IFN- $\alpha$  also may indirectly regulate the balance between Th1 and Th2 cell populations and, therefore, the innate and adaptive immune responses. Moreover, induction of IFN- $\alpha$  is independent of NF- $\kappa$ B activation.

Additionally, the production and secretion of NF- $\kappa$ B-dependent cytokines can be useful as reporters of cellular responses resulting from immunological challenge. Detection and measurement of such cytokines may provide comparative qualitative data regarding a cell's response to immunological challenge that is more relevant to an investigator than NF- $\kappa$ B activation data.

Thus, the present invention relates to assays designed to detect induction of immune system compounds. Such assays also may be useful for identifying compounds that induce expression of immune system compounds through TLRs. Parts of the following description are provided in the context of IFN- $\alpha$  induction and detection. However, many of the features of the embodiments described below also may be realized using assays designed to specifically detect or induce other immune system compounds. Thus, assays designed to specifically detect or induce other immune system compounds

having publicly available gene sequence information are explicitly included in the scope of the present invention.

### Assay Tools

5           The assays of the present invention employ a recombinant cell line capable of inducing gene expression from an expression control sequence of a gene that encodes an immune system compound (e.g., IFN- $\alpha$ ) in response to TLR activation. In some embodiments, for example, cells of the recombinant cell line, when exposed to a TLR agonist, can induce expression from an IFN- $\alpha$  promoter to a greater extent than cells of the  
10           corresponding untransfected cell line. Cells of the untransfected cell lines may substantially lack a functional level of TLR expression (i.e., untransfected cells may not detectably induce expression from the IFN- $\alpha$  promoter in response to exposure to a TLR agonist). Alternatively, cells of the untransfected cell line may exhibit a baseline level of background TLR function, but the baseline level is less than the level of TLR function  
15           observed in cells of the corresponding recombinant (i.e., transfected) cell line.

          Cells of certain recombinant cell lines include a first nucleic acid sequence that encodes a TLR operably linked to an expression control sequence. The cells also include a second nucleic acid sequence that encodes a reporter capable of generating a detectable signal when it is expressed in the recombinant cell under conditions suitable for generating  
20           the detectable signal. The reporter is linked to a second expression control sequence that is capable of being induced by activation of the TLR encoded by the first nucleic acid sequence.

          The TLR encoded by the first nucleic acid sequence, when present, may be any TLR. Ten different human TLRs have been identified, cloned, and sequenced. TLRs also  
25           are known to exist in other mammals including mice and chimpanzees. The nucleotide sequences of the ten human TLRs and many non-human TLRs are known, have been published, and are readily accessible from various sequence databases including GenBank. The first nucleic acid sequence may include any one of the TLRs for which the nucleotide sequence is known, whether human or non-human. In one embodiment, the TLR is human  
30           TLR6; in another embodiment, the TLR is human TLR7. Alternatively, the first nucleic acid may encode any one of the ten human TLRs, any non-human TLR, or any combination of two or more TLRs that may be desirable for a particular construct.



The first nucleic acid sequence, when present, can include a nucleotide sequence that differs from the specific published nucleotide sequence for the TLR encoded by the first nucleic acid sequence. For example, the first nucleic acid sequence can contain one or more substitutions (compared to a published TLR nucleotide sequence) that do not alter the amino acid sequence of the TLR protein expressed from the first nucleic acid sequence. Such a substitution may be termed a degenerate substitution. Nucleotide sequences containing one or more degenerate substitutions compared to a known TLR nucleotide sequence are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

As another example, certain nucleotide substitutions may alter the amino acid sequence of the TLR protein. For certain amino acid substitutions, however, the chemical properties of the protein having the altered amino acid sequence are similar to the chemical properties of the protein having the native amino acid sequence. Amino acids may be divided into four groups based on the chemical characteristics of the amino acid side groups: neutral, non-polar amino acids include glycine, alanine, valine, isoleucine, leucine, phenylalanine, proline, and methionine; neutral, polar amino acids include serine, threonine, tyrosine, tryptophan, asparagine, glutamine, and cysteine; acidic amino acids include aspartic acid and glutamic acid; and basic amino acids include lysine, arginine, and histidine. Substitution of one amino acid for another amino acid within the same group may have little or no functional effect on the resulting protein because of the similarity of the chemical characteristics of the amino acids involved in the substitution. Such amino acid substitutions may be termed a conservative amino acid substitution. Nucleotide sequences that, when compared to a known TLR nucleotide sequence, generate one or more conservative amino acid substitutions are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

The nucleic acid sequence that encodes a TLR, if present, may be cloned into an expression vector so that it is under the expression control of its own promoter, a homologous TLR promoter, or any heterologous promoter inducible in an appropriate host cell. For example, in certain embodiments, the TLR6 structural gene may be cloned into the commercially available mammalian expression vector pCI-neo. In this case, the TLR6 structural gene may be cloned into the vector's cloning region using the *NheI* and *MluI* restrictions sites. In such an embodiment, after transfection of the vector into a

mammalian cell, the TLR6 structural gene is under the transcriptional control of the vector's CMV enhancer/promoter region.

The second nucleic acid sequence encodes a reporter that is capable of generating a detectable signal when expressed in a host cell under conditions appropriate for generating the desired detectable signal. A wide variety of suitable reporter systems are known. For example, luciferase gene expression may generate a detectable luminescent signal under appropriate conditions. As another example,  $\beta$ -galactosidase expression can generate a detectable color change under appropriate conditions. As yet another example, production and secretion of an immune system compound may be detected by an enzyme-linked immunosorbent assay (ELISA). These and other reporter systems are known and assays for generating the detectable signals are commercially available.

The second nucleic acid sequence is operably linked to a second expression control sequence that includes a promoter sequence selected to be inducible by activation of a TLR. Thus, expression and activation of a TLR, whether naturally expressed by the recombinant cell or encoded by the first nucleic acid sequence, will induce gene expression from the second expression control sequence, thereby causing expression of the reporter, which may be detected by performing an assay designed to detect expression of the reporter. The second expression control sequence may include any suitable nucleotide sequence that can induce expression (e.g., a promoter) of a structural gene upon activation of the TLR encoded by the first nucleic acid sequence. Nucleotide sequences suitable for use as second expression control sequences include promoter sequences of TLR-inducible genes including but not limited to genes encoding cytokines, chemokines, co-stimulatory markers, and defensins. In certain embodiments, the second expression control sequence includes an IFN- $\alpha$ 1 promoter.

When the reporter system being employed to detect TLR activation includes detecting production and secretion of an immune system compound with an appropriate ELISA assay, the second expression control sequence may include the promoter of the gene encoding the immune system compounds being expressed and detected as the reporter. However, in certain embodiments, it may be desirable to express the immune system compound from a heterologous promoter.

When the gene expression system includes both a first nucleic acid sequence and a second nucleic acid sequence, the first nucleic acid sequence and the second nucleic acid

sequence may be contained within a single vector. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may be on separate vectors and co-transfected into a suitable host cell. In certain embodiments, for example, the first nucleic acid sequence may be cloned into the pCI-neo vector as described above, while the second  
5 nucleic acid sequence can be cloned into a reporter vector. One example of a commercially available reporter vector is the pGL3-Enhancer vector, which includes a luciferase reporter gene downstream of a cloning site for cloning a promoter sequence of interest. In some embodiments, the promoter of a TLR-inducible immune system compound may be cloned into the pGL3-Enhancer cloning site. In one such embodiment,  
10 the IFN- $\alpha$  promoter may be cloned into the pGL3-Enhancer cloning site.

Suitable host cells include any transfectable cells capable of expressing exogenous mammalian genes. In some embodiments, the host cells may be mammalian cells such as human cells or mouse cells. For example, suitable host cells include human cells or descendants of a human cell including but not limited to Namalwa cells or HEK293 cells.  
15 Alternatively, the host cells may be mouse cells or descendants of a mouse cell including but not limited to RAW 264.7 cells.

In one embodiment, the host cells include Namalwa cells. Namalwa cells have certain characteristics that may be particularly desirable for certain embodiments of the present invention. For example, Namalwa cells can include an expressible chromosomal  
20 IFN- $\alpha$  gene locus. Thus, upon appropriate stimulation (e.g., viral infection), Namalwa cells can be induced to produce and secrete IFN- $\alpha$  from the chromosomal IFN- $\alpha$  gene locus. However, Namalwa cells do not naturally express certain TLRs (e.g., TLR6, TLR7, or TLR9). Certain agonists of such TLRs have been shown to induce IFN- $\alpha$  expression in other cell types (e.g., PMBCs), but may not induce IFN- $\alpha$  expression in Namalwa cells  
25 unless a functional level of TLR expression is provided.

Namalwa cells transfected with an appropriate gene expression system may be capable of expressing a functional level of the TLR provided by the expression system. Thus, Namalwa cells transfected with an appropriate expression system may inducibly express IFN- $\alpha$  as a result of activating the cloned TLR (e.g., by exposure of the transfected  
30 Namalwa cells to an agonist). Thus, certain transfected cell lines permit one to identify a TLR agonist using an assay that detects TLR-mediated IFN- $\alpha$  expression by Namalwa cells.

Namalwa cells transfected with certain expression systems can provide alternative means of detecting TLR activation and, therefore, alternate assays for identifying TLR agonists. First, Namalwa cells transfected with an appropriate expression system may generate a detectable signal as a result of TLR-mediated expression of the expression system reporter (see Table 2). Second, Namalwa cells transfected with an expression system that provides functional TLR activity may provide TLR-mediated IFN- $\alpha$  expression from the chromosomal IFN- $\alpha$  gene locus.

### Assays

Assays according to the present invention may be performed using any suitable recombinant cell line. The recombinant cell line may be constructed by transfecting any suitable expression system into any suitable host cell. In the description of particular assays that follow, certain assay tools such as particular recombinant cell lines, particular gene expression systems, or particular host cells may be identified. However, many alternative assay tools may provide the features of the tools specifically identified and, consequently, may be suitable for use in assays according to the present invention. Such alternative embodiments are explicitly included in the scope of the present invention.

Also, each assay may or may not be performed in conjunction with one or more appropriate controls. Controls may be performed to assist in quantifying results or to ensure that the assay is performing as intended. However, with experience, one skilled in the art may develop sufficient familiarity with a particular assay that performing a control may not always be necessary to perform an assay of the present invention.

In some embodiments, assays according to the present invention may be designed to detect activation of a TLR. Such assays include providing a recombinant cell line having an appropriate gene expression system. Generally, an appropriate gene expression system includes a reporter that is (a) capable of generating a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions that are appropriate for generating the detectable signal, and (b) operably linked to an expression control sequence that is capable of being induced by an activated TLR. The assays also include exposing the recombinant cell line to a TLR agonist, thereby activating the TLR and inducing expression of the reporter from the TLR-inducible expression control sequence; providing conditions appropriate for generating the reporter's detectable signal, thereby

generating a detectable signal from the expressed reporter; and detecting the detectable signal, thereby detecting activation of the TLR.

In certain embodiments, the expression control sequence to which the reporter is operably linked may be a promoter of a TLR-inducible protein including but not limited to a cytokine, a chemokine, a co-stimulatory marker, or a defensin.

The recombinant cell line may be derived from a host cell that naturally expresses a functional level of one or more TLRs. In such embodiments, the gene expression system is not required to include a nucleic acid sequence that encodes a TLR. However, the gene expression system may include a nucleic acid sequence that encodes a TLR. For such assays, it may be desirable to measure any background level of detectable signal generated by the recombinant cell line before transfection with the nucleic acid sequence that encodes the TLR. In this way, one can obtain an indication of the extent of the detectable signal that is attributable to activation of the TLR expressed from the expression system if such an indication is desired.

When the gene expression system includes a nucleic acid sequence that encodes a TLR, one may select any TLR from any species for inclusion in the expression system. Accordingly, the nucleic acid sequence that encodes the TLR may include any one of the published TLR nucleotide sequences, any nucleotide sequence containing one or more degenerate variants of a published TLR nucleotide sequence, any nucleotide sequence that encodes a published TLR amino acid sequence, or any nucleotide sequence that encodes a protein having one or more conservative amino acid substitutions compared to a published TLR amino acid sequence.

In some embodiments in which the recombinant cell line includes a nucleic acid sequence encoding a TLR, a single vector may contain a first nucleic acid sequence that encodes the reporter and a second nucleic acid sequence that encodes the TLR. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may exist on separate vectors so that the host cells must be co-transfected with both vectors in order for the recombinant cell line to include entire gene expression system.

The gene expression system may include any suitable reporter operably linked to any suitable TLR-inducible expression control sequence. Suitable reporters are described in the detailed description of the gene expression system included in the description of assay tools provided above.

In one particular embodiment, the recombinant cell line is derived from the human lymphoblastoid Namalwa cell line. Namalwa cells lack a functional level of TLR6 activity. The recombinant cell line is obtained by co-transfecting Namalwa cells with two vectors that, together, provide a gene expression system: the first vector includes a nucleic acid sequence that encodes human TLR6 operably linked to an expression control  
5 sequence; the second vector contains a nucleic acid sequence that encodes a luciferase reporter gene that is operably linked to an IFN- $\alpha$  promoter. The IFN- $\alpha$  promoter is inducible by activation of TLR6. A culture of the recombinant cells is contacted with an agonist of TLR6, thereby activating TLR6 that has been expressed from the first vector of  
10 gene expression system. The activation of TLR6 induces expression from the IFN- $\alpha$  promoter on the second vector of the gene expression system. Expression from the IFN- $\alpha$  promoter results in expression of the luciferase reporter gene. The recombinant cells, which are now expressing the luciferase reporter, are contacted with a luciferase reagent that generates a luminescent signal when allowed to react with luciferase. Detection of the  
15 luminescent signal indicates expression of the luciferase reporter from the IFN- $\alpha$  promoter that, in turn, indicates activation of TLR6.

As indicated above in the detailed description of the assay tools, various suitable reporter systems may be used in alternative embodiments of assays according to the present invention. Also as indicated above, one feature of constructing the recombinant  
20 cell line from Namalwa host cells is the cells can produce and secrete IFN- $\alpha$  expressed from the chromosomal IFN- $\alpha$  gene locus of the Namalwa cell. Thus, detection of IFN- $\alpha$  production (e.g., by ELISA) may be used as a reporter of TLR activation. When used in conjunction with a reporter encoded by the gene expression system, the use of two independent reporters may provide certain embodiments of the assays of the present  
25 invention with an internal control.

In some alternative embodiments, assays according to the present invention may be designed to identify agonists of a particular TLR. Generally, such assays include providing a recombinant cell line constructed by transfecting host cells with a gene expression system that includes (a) a first nucleic acid sequence that encodes a particular  
30 TLR, and (b) a second nucleic acid sequence that encodes a reporter operably linked to an expression control sequence that is inducible by activation of the TLR encoded by the expression system. The assays also include contacting cell cultures of the recombinant

cell line with one or more test compounds, and then exposing the cell cultures to conditions effective for generating a detectable signal from the reporter in the event that the reporter is expressed. Detection of a TLR-mediated detectable signal indicates that expression of the reporter is at least partially attributable to activation of the TLR by the test compound, thereby identifying the test compound as an agonist of the TLR.

As with the assays described above that are designed for detecting TLR activation, assays for detecting TLR agonists include a gene expression system that may include one or more vectors, a nucleic acid sequence that encodes any suitable reporter, and any suitable TLR-inducible expression control sequence. Furthermore, the gene expression system can include a nucleic acid sequence that encodes any particular TLR. Thus, an assay may be designed to identify agonists of any particular TLR.

Detection of a TLR-mediated detectable signal may include a determination of background detectable signal generated by the recombinant cell line prior to transfection with a nucleic acid sequence that encodes a particular TLR. A recombinant cell line may, in some embodiments, naturally possess a certain level of TLR expression that can induce expression of the reporter, thereby generating background signal. Alternatively, background expression of the reporter may result from induction of the expression control sequence that regulates expression of the reporter coming from an alternative (i.e., non-TLR) source. Once a background level of detectable signal is determined for the recombinant cell line, it may not be necessary to determine the background signal generation every time the assay is performed.

In one particular embodiment, the recombinant cell line includes Namalwa cells, cells that lack a functional level of natural TLR6 expression. The recombinant cell line is constructed by co-transfecting Namalwa cells with a gene expression system that includes two vectors: a first vector that includes a first nucleic acid sequence that encodes human TLR6 operably linked to an expression control sequence; and a second vector that includes a second nucleic acid sequence that encodes a luciferase reporter operably linked to an IFN- $\alpha$  promoter. The first nucleic acid sequence permits the recombinant cells to functionally express TLR6. The second nucleic acid sequence allows one to detect activation of the TLR6 expressed from the first nucleic acid sequence.

In this particular embodiment, a culture of the recombinant cells is dispensed into wells of a multi-well test plate. A different test compound is added to each well. A test

compound that acts as a TLR6 agonist will activate the TLR6 expressed from the first vector of the gene expression system, thereby inducing expression from the IFN- $\alpha$  promoter operably linked to the luciferase reporter on the second vector of the gene expression system. The recombinant cells, which are now expressing the luciferase reporter, are contacted with a luciferase reagent that generates a TLR-mediated detectable signal only when the luciferase reporter is expressed. Detection of a TLR-mediated detectable signal in a particular well of the multi-well plate indicates expression of the luciferase reporter from the IFN- $\alpha$  promoter that, in turn, indicates activation of TLR6 by the test compound added to the recombinant cells in that well. A test compound that  
5  
10 activates TLR6 is an agonist of TLR6.

Test compounds may be added to wells containing recombinant cells in any manner appropriate for the design of a particular assay. For example, the same test compound may be added to each of a plurality of wells, thereby generating multiple data points for that test compound. Alternatively, a different test compound may be added to  
15 each well. In this way, the number of test compounds that can be screened in a single assay can be maximized. In some embodiments, test compound may even be omitted from a certain number of wells, e.g., in order to generate one or more controls.

In another particular embodiment, the assay may be designed to identify agonists of TLR7 by designing the recombinant cell line to include a gene expression system that includes a nucleic acid sequence that encodes human TLR7. In all other respects, the  
20 assay may be performed as described above for the detection of TLR6 agonists.

Additional alternative embodiments include assays that are designed to identify agonists of any one of the human TLRs or any non-human TLR merely by designing the gene expression system to include a nucleic acid sequence that encodes the desired TLR.  
25

The present invention also provides TLR agonist compounds identified using an assay according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to design assays that can identify TLR agonists that are not detectable using previously known TLR activation assays. The TLR agonists may include chemical structures similar in certain  
30 respects to the chemical structures of known IRM compounds. Alternatively, assays according to the present invention may be used for screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR



agonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR agonist identified using an assay according to the present invention, or a  
5 pharmaceutically acceptable salt thereof, in an amount effective for inducing a TLR-mediated cellular response.

In still other embodiments, assays according to the present invention may be designed to identify antagonists of a particular TLR. Generally, an assay may be designed to identify an antagonist of a particular TLR by designing the recombinant cell line to  
10 include a gene expression system having (a) a first nucleic acid sequence that encodes a particular TLR, and (b) a second nucleic acid sequence that encodes a reporter operably linked to a TLR-inducible expression control sequence. Aliquots of the recombinant cell line may be dispensed into wells of a multi-well test plate. A different test compound can be added to each well, and then a known agonist of the particular TLR can be added to  
15 each well. In such assays, the agonist of the particular TLR will induce expression of the reporter and generation of a detectable signal unless the test compound acts as an antagonist of the particular TLR. Therefore, antagonists of the particular TLR can be identified by detecting wells exhibiting something less than a full TLR-mediated detectable signal.

20 As with the assays described above that are designed for identifying TLR agonists, assays for detecting TLR antagonists include a gene expression system that may include one or more vectors, a nucleic acid sequence that encodes any suitable reporter, any suitable TLR-inducible expression control sequence, and a nucleic acid sequence that encodes any particular TLR. Thus, an assay may be designed to identify antagonists of  
25 any particular TLR.

In one particular embodiment, an assay that identifies antagonists of human TLR6 may be designed using the recombinant cell line described above for the identification of TLR6 agonists. The recombinant cells are dispensed into the wells of a multi-well test plate. A different test compound is added to each well. A known TLR6 agonist such as  
30 any one of the IRM compounds listed in Table 1 can be added to each well.

Generation and detection of the TLR-mediated detectable signal can be performed as described above for assays designed to detect TLR activation or identify TLR agonists.

The TLR-mediated detectable signal from each well can be compared to a standard full TLR-mediated detectable signal or to a positive control. Test compounds that inhibit the TLR-mediate detectable signal compared to the standard or the positive control can be identified as antagonists of TLR6.

5           In alternative embodiments, test compounds may be added to the wells in any desired manner, as described above with regard to assays designed to identify TLR agonists.

Other alternative embodiments include assays designed to identify antagonists of any one of the human TLRs or any non-human TLR. Such alternative embodiments may  
10           be performed by designing the gene expression system to include a nucleic acid sequence that encodes the desired TLR.

The present invention also provides TLR antagonist compounds identified using an assay according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to design assays  
15           that can identify TLR antagonists that are not detectable using previously known TLR activation assays. The TLR antagonists may include chemical structures similar in certain respects to the chemical structures of known IRM compounds. Alternatively, assays according to the present invention may be used for screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR  
20           antagonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR antagonist identified using an assay according to the present invention, or a pharmaceutically acceptable salt thereof, in an amount effective for inhibiting a TLR-  
25           mediated cellular response.

### Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however,  
30           that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

### Construction of vectors

The vector pIFN- $\alpha$ 1-luc was constructed by inserting BglII sites at both ends of the human IFN- $\alpha$ 1 promoter (SEQ ID NO:21). The BglII sites were inserted into the IFN- $\alpha$ 1  
5 promoter and the sequence was amplified using the primer pair of SEQ ID NO:22 and SEQ ID NO:23. The amplified IFN- $\alpha$ 1 promoter was cloned into the pGL3-Enhancing vector (Promega Corp., Madison, WI) at the BglII site.

The vector pCI-TLR6 was constructed by inserting SEQ ID NO:11 (GenBank Accession No. NM 006068), which includes the human TLR6 coding sequence, into the  
10 pCI-neo mammalian expression vector (Promega Corp.) at the vector's NheI and MluI restriction sites.

### Transfections

Unless otherwise indicated, all incubations were performed at 37°C with 5% CO<sub>2</sub>  
15 at 98% humidity.

Culture medium was prepared from complete RPMI 1640 medium (BioSource International, Inc., Camarillo, CA). Fetal bovine serum (Atlas Biologicals, Inc., Ft. Collins, CO) was added to a final concentration of 7.5% (vol/vol); L-glutamine (BioSource International, Inc.) was added to 5 mM; and sodium pyruvate (BioSource  
20 International, Inc.) was added to 1 mM.

Burkitt's Lymphoma lymphoblastoid Namalwa cells (ATCC Accession No. CRL-1432) were grown by incubation in culture medium overnight. Cells were harvested by centrifugation in a tabletop centrifuge (1200 RPM for 5 minutes), and then resuspended in phosphate buffered sucrose to a concentration of  $1.3 \times 10^7$  cells per milliliter.

25 For each transfection, a 750  $\mu$ L aliquot of the cell suspension was placed in an electroporation cuvette with 4 mm gaps. 10  $\mu$ g of the pIFN- $\alpha$ 1-luc vector and 10  $\mu$ g of the pCI-TLR6 vector were added to the electroporation cuvette. The cell and vector mixtures were incubated at room temperature for 5 minutes. The cells were electroporated using a BioRad Gene Pulser (BioRad Laboratories, Hercules, CA) set to at 500  $\mu$ F capacitance  
30 and 0.27 volts, then incubated at room temperature for 5 minutes.

The electroporated cells were suspended in 10 mLs of culture medium and incubated overnight. Dead cells and debris were removed after 24 hours using a MACS

Dead Cell Removal kit (Miltenyi Biotec, Auburn, CA). Cells were resuspended in 10 mLs of culture medium and incubated for an additional 24 hours.

Transfected cells were selected by adding G418 (Promega Corp., Madison, WI) to a final concentration of 1 mg/mL and incubating the cells for seven days.

5

### Assays

The selected transfected cells were counted and resuspended to a concentration of  $1 \times 10^6$  cell per mL in culture medium. 100  $\mu$ L aliquots of cells were placed in the wells of a white-walled, white-bottomed 96-well plate (Corning, Inc. Corning, NY). 1.0  $\mu$ L of an IRM compound from Table 1 (prepared at 1 mM in 100% DMSO) was added to some cell aliquots so that the final concentration of IRM compound was 10  $\mu$ M. As a positive control, some cell aliquots were incubated with Sendai virus instead of IRM compound. As a negative control, some cell aliquots were incubated with DMSO without IRM compound. In all cases, the cells were incubated for 18 hours.

15

**Table 1 - IRM Compounds**

| Compound | Chemical Name   | Citation                     |
|----------|---|------------------------------|
| IRM 1    | 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-6,7,8,9-tetrahydro-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinoline-1-ethanol                   | U.S. 5,352,784<br>Example 91 |
| IRM 2    | 4-amino- $\alpha,\alpha,2$ -trimethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinoline-1-ethanol  | U.S. 5,266,575<br>Example C1 |
| IRM 3    | N-[4-(4-amino-2-butyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)butyl]methanesulfonamide   | U.S. 6,331,539<br>Example 6  |
| IRM 4    | 1-{2-[3-(3-pyridyl)propoxy]ethyl}-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-4-amine   | WO 02/46193<br>Example 33    |
| IRM 5    | 2-butyl-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ][1,5]naphthyridin-4-amine   | U.S. 6,194,425<br>Example 39 |
| IRM 6    | 2-butyl-6,7,8,9-tetrahydro-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ][1,5]naphthyridin-4-amine                                    | U.S. 6,194,425<br>Example 40 |
| IRM 7    | N <sup>3</sup> -(4-[4-amino-2-(2-methoxyethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl]butyl)-6-(1 <i>H</i> -1-pyrrolyl)nicotinamide | U.S. 6,451,810<br>Example 60 |
| IRM 8    | 2-ethyl-1-[5-(methylsulfonyl)pentyl]-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-4-amine  | WO 02/46192<br>Example 13    |

The plates were equilibrated to room temperature before 1 volume of reconstituted LucLight Plus (Packard Instruments, Meriden, CT) was added to each aliquot of cells. Each well of the plate was read on an LJI Analyst (LJI Biosystems, Inc., Sunnyvale, CA) set with a 5 minute dark adapt. Data from a representative experiment are shown in Table 2. The data are expressed as the fold increase in luciferase induction off of the IFN- $\alpha$ 1 promoter in cell aliquots incubated with the indicated stimulant compared to the negative control in which the cell aliquots were incubated with only DMSO.

Table 2 - TLR Expression by pIFN- $\alpha$ 1-luc/pCI-TLR6 Co-Transfected Namalwa cells

| <b>Stimulant</b> | <b>Fold Increase in Luciferase Induction</b> |
|------------------|--|
| IRM1             | 3.6  |
| IRM2             | 2.7  |
| IRM3             | 2.6  |
| IRM4             | 4.0  |
| IRM5             | 3.2  |
| IRM6             | 2.9  |
| IRM7             | 3.2  |
| IRM8             | 2.3  |
| Sendai virus     | 2.7  |

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is Claimed is:

1. A method of detecting activation of a TLR in a cell comprising:  
providing a cell culture comprising cells transfected with a nucleic acid sequence  
that encodes a reporter that (a) generates a detectable signal when the reporter is expressed  
5 and the cell is exposed to conditions effective for generating the detectable signal, and (b)  
is operably linked to an expression control sequence that is induced by activation of a TLR  
and comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker  
promoter, or a defensin promoter;  
exposing the cell culture to a compound that activates a TLR;  
10 providing conditions effective for generating the detectable signal; and  
detecting the detectable signal.
2. The method of claim 1 wherein the expression control sequence comprises an IFN-  
 $\alpha$  promoter.
- 15 3. The method of claim 1 wherein the detectable signal comprises luciferase activity,  
 $\beta$ -galactosidase activity, or a positive signal from an enzyme-linked immunosorbent assay.
4. The method of claim 1 wherein the cell culture comprises mammalian cells or  
20 descendants of a mammalian cell.
5. The culture cell of claim 4 wherein the cell culture comprises human cells or  
descendants of a human cell.
- 25 6. The method of claim 1 wherein the cells are further transfected with a second  
nucleic acid sequence that encodes a TLR operably linked to a second expression control  
sequence.
- 30 7. The method of claim 6 wherein the first nucleic acid sequence comprises the  
nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ  
ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID  
NO:19, or a degenerate variant of any of the foregoing.

8. The method of claim 6 wherein the first nucleic acid sequence comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID  
5 NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.

9. The method of claim 6 wherein the nucleic acid sequence that encodes the reporter and the second nucleic acid sequence are contained on a single vector.  
10

10. The method of claim 6 wherein the nucleic acid sequence that encodes the reporter is contained on a first vector and the second nucleic acid sequence is contained on a second vector.

15 11. A method of identifying a TLR agonist comprising:  
providing a cell culture comprising cells transfected with:  
a first nucleic acid sequence that comprises a nucleotide sequence that encodes a TLR operably linked to a first expression control sequence and  
a second nucleic acid sequence that encodes a reporter that (a) generates a  
20 detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that is induced by activation of a TLR;  
contacting the cell culture with a test compound;  
providing conditions effective for generating the detectable signal, thereby  
25 generating a TLR-mediated detectable signal; and  
identifying the compound as an agonist of the TLR if a TLR-mediated detectable signal is detected.

12. The method of claim 11 wherein the first nucleic acid sequence comprises the  
30 nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, or a degenerate variant of any of the foregoing.

13. The method of claim 11 wherein the first nucleic acid sequence comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.
14. The method of claim 11 wherein the second expression control sequence comprises an IFN- $\alpha$  promoter.
15. The method of claim 11 wherein the detectable signal comprises luciferase activity,  $\beta$ -galactosidase activity, or a positive signal from an enzyme-linked immunosorbent assay.
16. The method of claim 11 wherein the cell culture comprises mammalian cells or descendents of a mammalian cell.
17. The method of claim 16 wherein the cell culture comprises human cells or descendents of a human cell.
18. The method of claim 11 wherein the first nucleic acid sequence and the second nucleic acid sequence are included in a single vector.
19. The method of claim 11 wherein the first nucleic acid sequence and the second nucleic acid sequence are located on separate vectors.
20. The method of claim 19 wherein the cell culture comprises cells co-transfected with the separate vectors.
21. The method of claim 11 wherein the cell culture comprises cells that, prior to transfection with the first nucleic acid sequence, exhibit no detectable function of the Toll-like receptor encoded by the first nucleic acid sequence.



22. The method of claim 11 wherein the second expression control sequence comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter
- 5
23. A TLR agonist identified by the method of claim 11.
24. A pharmaceutical composition comprising a TLR agonist identified by the method of claim 23 or a pharmaceutically acceptable salt thereof.
- 10
25. A method of identifying an antagonist of a TLR comprising:  
providing a cell culture that comprises cells transfected with:  
a first nucleic acid sequence that comprises a nucleotide sequence that encodes the TLR operably linked to a first expression control sequence, and  
15 a second nucleic acid sequence that encodes a reporter that (a) is operably linked to a second expression control sequence that is induced by activation of the TLR, and (b) generates a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective for generating the detectable signal;  
contacting the cell culture with an agonist of the TLR and a test compound;  
20 providing conditions effective for generating the detectable signal, thereby permitting the cell culture to generate a full TLR-mediated detectable signal in the absence of an antagonist of the TLR;  
measuring the detectable signal; and  
identifying the compound as an antagonist of the TLR if the detectable signal is  
25 less than a full TLR-mediated detectable signal.
26. A TLR antagonist identified by the method of claim 25.
27. A pharmaceutical composition comprising a TLR antagonist identified by the method of claim 26 or a pharmaceutically acceptable salt thereof.
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Asn Ile Leu Thr Asp Thr Ile Phe Arg Cys Leu Pro Pro Arg Ile Lys  
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Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser Ile Pro Lys Gln Val  
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Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val Ala Phe Asn Ser Leu  
 465 470 475 480

Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser Leu Ser Val Leu Ile  
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Ile Asp His Asn Ser Val Ser His Pro Ser Ala Asp Phe Phe Gln Ser  
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Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp Asn Pro Phe Gln Cys  
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Thr Cys Glu Leu Gly Glu Phe Val Lys Asn Ile Asp Gln Val Ser Ser  
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Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys Cys Asp Tyr Pro Glu  
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Ser Tyr Arg Gly Thr Leu Leu Lys Asp Phe His Met Ser Glu Leu Ser  
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Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Val Ala Thr Met Leu Val  
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Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr Leu Asp Leu Pro Trp  
595 600 605

Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr Arg Arg Arg Ala Arg  
610 615 620

Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe  
625 630 635 640

Ile Ser Tyr Ser Gly His Asp Ser Phe Trp Val Lys Asn Glu Leu Leu  
645 650 655

Pro Asn Leu Glu Lys Glu Gly Met Gln Ile Cys Leu His Glu Arg Asn  
660 665 670

Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Thr Cys Ile Glu  
675 680 685

Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Ser  
690 695 700

Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His  
705 710 715 720

Glu Gly Ser Asn Ser Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln  
725 730 735

Tyr Ser Ile Pro Ser Ser Tyr His Lys Leu Lys Ser Leu Met Ala Arg  
740 745 750

Arg Thr Tyr Leu Glu Trp Pro Lys Glu Lys Ser Lys Arg Gly Leu Phe  
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Lys Lys  
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58183US002.ST25.txt

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accagtcttt gtctagttgg gatctttatg tctagtagtta tagttaagtt cattcagaca 2580
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Asn Gly Ile Cys Lys Gly Ser Ser Gly Ser Leu Asn Ser Ile Pro Ser  
35 40 45

Gly Leu Thr Glu Ala Val Lys Ser Leu Asp Leu Ser Asn Asn Arg Ile  
50 55 60



## 58183US002.ST25.txt

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 85 90 95  
 Ser Ser Leu Gly Ser Leu Glu His Leu Asp Leu Ser Tyr Asn Tyr Leu  
 100 105 110  
 Ser Asn Leu Ser Ser Ser Trp Phe Lys Pro Leu Ser Ser Leu Thr Phe  
 115 120 125  
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 130 135 140  
 Phe Ser His Leu Thr Lys Leu Gln Ile Leu Arg Val Gly Asn Met Asp  
 145 150 155 160  
 Thr Phe Thr Lys Ile Gln Arg Lys Asp Phe Ala Gly Leu Thr Phe Leu  
 165 170 175  
 Glu Glu Leu Glu Ile Asp Ala Ser Asp Leu Gln Ser Tyr Glu Pro Lys  
 180 185 190  
 Ser Leu Lys Ser Ile Gln Asn Val Ser His Leu Ile Leu His Met Lys  
 195 200 205  
 Gln His Ile Leu Leu Leu Glu Ile Phe Val Asp Val Thr Ser Ser Val  
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 225 230 235 240  
 Glu Leu Ser Thr Gly Glu Thr Asn Ser Leu Ile Lys Lys Phe Thr Phe  
 245 250 255  
 Arg Asn Val Lys Ile Thr Asp Glu Ser Leu Phe Gln Val Met Lys Leu  
 260 265 270  
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 275 280 285  
 Leu Asn Gly Val Gly Asn Phe Arg Ala Ser Asp Asn Asp Arg Val Ile  
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 305 310 315 320  
 Page 8

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 325 330 335  
 Arg Val Lys Arg Ile Thr Val Glu Asn Ser Lys Val Phe Leu Val Pro  
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 Cys Leu Leu Ser Gln His Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser  
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 Glu Asn Leu Met Val Glu Glu Tyr Leu Lys Asn Ser Ala Cys Glu Asp  
 370 375 380  
 Ala Trp Pro Ser Leu Gln Thr Leu Ile Leu Arg Gln Asn His Leu Ala  
 385 390 395 400  
 Ser Leu Glu Lys Thr Gly Glu Thr Leu Leu Thr Leu Lys Asn Leu Thr  
 405 410 415  
 Asn Ile Asp Ile Ser Lys Asn Ser Phe His Ser Met Pro Glu Thr Cys  
 420 425 430  
 Gln Trp Pro Glu Lys Met Lys Tyr Leu Asn Leu Ser Ser Thr Arg Ile  
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 His Ser Val Thr Gly Cys Ile Pro Lys Thr Leu Glu Ile Leu Asp Val  
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 485 490 495  
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 Thr Phe Ser Lys Glu Gln Leu Asp Ser Phe His Thr Leu Lys Thr Leu  
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 530 535 540  
 Thr Gln Glu Gln Gln Ala Leu Ala Lys Val Leu Ile Asp Trp Pro Ala  
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 Asn Tyr Leu Cys Asp Ser Pro Ser His Val Arg Gly Gln Gln Val Gln  
 Page 9

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565

570

575

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                   595                  600                  605

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                   610                  615                  620

Leu Gln Ala Lys Arg Lys Pro Arg Lys Ala Pro Ser Arg Asn Ile Cys  
                   625                  630                  635                  640

Tyr Asp Ala Phe Val Ser Tyr Ser Glu Arg Asp Ala Tyr Trp Val Glu  
                   645                  650                  655

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Cys Leu His Lys Arg Asp Phe Ile Pro Gly Lys Trp Ile Ile Asp Asn  
                   675                  680                  685

Ile Ile Asp Ser Ile Glu Lys Ser His Lys Thr Val Phe Val Leu Ser  
                   690                  695                  700

Glu Asn Phe Val Lys Ser Glu Trp Cys Lys Tyr Glu Leu Asp Phe Ser  
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His Phe Arg Leu Phe Asp Glu Asn Asn Asp Ala Ala Ile Leu Ile Leu  
                   725                  730                  735

Leu Glu Pro Ile Glu Lys Lys Ala Ile Pro Gln Arg Phe Cys Lys Leu  
                   740                  745                  750

Arg Lys Ile Met Asn Thr Lys Thr Tyr Leu Glu Trp Pro Met Asp Glu  
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| agtgcactgt tagccatgaa gttgctgact gcagccacct gaagttgact caggtacccg  | 240  |
| atgatctacc cacaaacata acagtgttga accttaccca taatcaactc agaagattac  | 300  |
| cagccgccaa cttcacaagg tatagccagc taactagctt ggatgtagga tttaacacca  | 360  |
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| agaatttaac cacattagat ctgtctcata atggcttgct atctacaaaa ttaggaactc  | 600  |
| aggttcagct ggaaaatctc caagagcttc tattatcaaa caataaaatt caagcgctaa  | 660  |
| aaagtgaaga actggatatc ttgtccaatt catctttaa aaaattagag ttgtcatcga   | 720  |
| atcaaatata agagttttct ccagggtgtt ttcacgcaat tggaagatta tttggcctct  | 780  |
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| acacaagcat tcggaatctg tctctgagta acagccagct gtccaccacc agcaatacaa  | 900  |
| ctttcttggg actaaagtgg acaaatctca ctatgctcga tctttcctac aacaacttaa  | 960  |
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| aactaaagat catcgattta ggattgaata atttaaacac acttccagca tctgtcttta  | 1920 |
| ataatcaggt gtctctaaag tcattgaacc ttcagaagaa tctcataaca tccgttgaga  | 1980 |

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 35 40 45

Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg  
 50 55 60

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58183US002.ST25.txt

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 85 90 95

Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser  
 100 105 110

Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu  
 115 120 125

His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val  
 130 135 140

Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser  
 145 150 155 160

Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu  
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 180 185 190

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 195 200 205

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Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys  
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Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser  
 245 250 255

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 260 265 270

Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val  
 275 280 285

Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe  
 290 295 300

Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly  
 305 310 315 320

Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln  
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58183US002.ST25.txt

325

330

335

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 385 390 395 400  
 Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys  
 405 410 415  
 Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His  
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 435 440 445  
 Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser  
 450 455 460  
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58183US002.ST25.txt  
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Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn  
595 600 605

Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser  
610 615 620

Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu  
625 630 635 640

Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp  
645 650 655

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Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val  
675 680 685

Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu  
690 695 700

Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val  
705 710 715 720

Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val  
725 730 735

Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu  
740 745 750

Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp  
755 760 765

Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu  
770 775 780

Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu  
785 790 795 800

Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val  
805 810 815

Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val  
820 825 830



## 58183US002.ST25.txt

His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile  
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Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu  
       850                          855                          860

Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro  
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Val Gln Lys Glu Arg Ile Gly Ala Phe Arg His Lys Leu Gln Val Ala  
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58183US002.ST25.txt

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| ccacattgaa actcaaatct ctcaaaaggc ttactttcac ttccaacaaa ggtggggaatg  | 1260 |
| ctttttcaga agttgatcta ccaagccttg agttttctaga tctcagtaga aatggccttga | 1320 |
| gtttcaaagg ttgctgttct caaagtgatt ttgggacaac cagcctaaag tatttagatc   | 1380 |
| tgagcttcaa tgggtgttatt accatgagtt caaacttctt gggccttagaa caactagaac | 1440 |
| atctggattt ccagcattcc aatttgaaac aaatgagtga gttttcagta ttcctatcac   | 1500 |
| tcagaaacct catttacctt gacattttct atactcacac cagagttgct ttcaatggca   | 1560 |
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| gtcaactgga gcagttgtct ccaacagcat ttaactcact ctccagtctt caggtagtaa   | 1740 |
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| tccaggttct tgattacagt ctcaatcaca taatgacttc caaaaaacag gaactacagc   | 1860 |
| atthttccaag tagtctagct ttcttaaatc ttactcagaa tgactttgct tgtacttggtg | 1920 |
| aacaccagag tttcctgcaa tggatcaagg accagaggca gctcttggtg gaagttgaac   | 1980 |
| gaatggaatg tgcaaacact tcagataagc agggcatgcc tgtgctgagt ttgaatatca   | 2040 |
| cctgtcagat gaataagacc atcattgggtg tgtcggctct cagtgtgctt gtagtatctg  | 2100 |
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| agtatggtag aggtgaaaac atctatgatg cctttgttat ctactcaagc caggatgagg   | 2220 |
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| gccttcacta cagagacttt attcccgggtg tggccattgc tgccaacatc atccatgaag  | 2340 |
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| gggtgatctt tgaatatgag attgtctcaga cctggcagtt tctgagcagt cgtgctggta  | 2460 |
| tcattctcat tgtcctgcag aagggtggaga agacctgct caggcagcag gtggagctgt   | 2520 |
| accgccttct cagcaggaac acttacctgg agtgggagga cagtgtcctg gggcggcaca   | 2580 |
| tcttctggag acgactcaga aaagccctgc tggatggtaa atcatggaat ccagaaggaa   | 2640 |
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| cctcctgagg catttcttgc ccagctgggt ccaacacttg ttcagttaat aagtattaaa   | 2760 |
| tgctgccaca tgtcaggcct tatgctaagg gtgagtaatt ccatgggtgca ctagatatgc  | 2820 |
| agggctgcta atctcaagga gcttccagt cagaggggaat aaatgctaga ctaaaataca   | 2880 |
| gagtcttcca ggtgggcatt tcaaccaact cagtcaagga acccatgaca aagaaagtca   | 2940 |
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## 58183US002.ST25.txt

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Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys  
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Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu  
 50 55 60

Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly  
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Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr  
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Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu  
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 225 230 235 240  
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 Page 19

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 Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu  
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 Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr  
 580 585 590  
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58183US002.ST25.txt

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Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr  
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Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu  
 645 650 655

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe  
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Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His  
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Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser  
 690 695 700

Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu  
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Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys  
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Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn  
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Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp  
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## 58183US002.ST25.txt

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Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys  
 35 40 45

Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln  
 50 55 60

Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe  
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58183US002.ST25.txt

Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn  
85 90 95

Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly  
100 105 110

Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp  
115 120 125

Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr  
130 135 140

Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln  
145 150 155 160

Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His  
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Lys Leu Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp  
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## 58183US002.ST25.txt

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| gaata   | tctca  | atattt   | taca     | ttta     | acaata   | attgaa  | agca     | ttcgt   | gaaga   | agatt  | tttact   | 960  |
| tattct  | aaaa   | cgacatt  | gaa      | agcatt   | gaca     | ataga   | acata    | tcacga  | acca    | agtttt | tctg     | 1020 |
| ttttc   | acaga  | cagcttt  | gta      | caccgt   | gttt     | tctga   | gatga    | acattat | gat     | gtta   | accatt   | 1080 |
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| acgaag  | gata   | tgcttt   | cttt     | ggaa     | atactg   | gatgt   | tagct    | ggaat   | tcttt   | ggaat  | ctggt    | 1320 |
| agacata | aaag   | aaaact   | gcac     | ttggg    | ttgag    | agtata  | gtg      | gttaa   | at      | tt     | gtcttcaa | 1380 |
| atgctt  | actg   | tttt     |          | cagat    | gttta    | cctccc  | cagga    | tcaag   | gtact   | tgat   | ctttcac  | 1440 |
| agcaata | aaaa   | taaag    | agcgt    | tccta    | aaaca    | gtcgt   | aaaac    | tgga    | agcttt  | gca    | agaactc  | 1500 |
| aatgtt  | gctt   | tcaatt   | cttt     | aactga   | cctt     | cctgg   | atgtg    | gcag    | ctttag  | cagc   | ctttct   | 1560 |
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| cagaag  | atga   | ggtca    | ataaa    | agcag    | gggac    | aatcc   | attcc    | aatgt   | acctg   | tgag   | ctaaga   | 1680 |
| gaattt  | gtca   | aaaat    | ataga    | ccaag    | tatca    | agtga   | agtgt    | tagag   | ggctg   | gcct   | gattct   | 1740 |
| tataag  | tgtg   | actacc   | caga     | aagtt    | ataga    | ggaag   | cccac    | taaag   | gactt   | tcac   | atgtct   | 1800 |
| gaattat | cct    | gcaac    | ataac    | tctg     | ctgatc   | gtcacc  | atcg     | gtgcc   | accat   | gctg   | ggtgtg   | 1860 |
| gctgtg  | actg   | tgacct   | ccct     | ctgcat   | ctac     | ttgg    | atctgc   | cctgg   | tattct  | cagg   | atggtg   | 1920 |
| tgccag  | tgga   | cccag    | actcg    | gcg      | cagggcc  | agga    | acatac   | ccttag  | aaga    | actc   | caaaga   | 1980 |
| aacctc  | cagt   | ttcat    | gcttt    | tattt    | catat    | agtga   | acatg    | attct   | gcctg   | ggtg   | aaaagt   | 2040 |
| gaattg  | gtac   | cttac    | ctaga    | aaa      | agaagat  | atac    | agattt   | gtctt   | catga   | gagga  | acttt    | 2100 |
| gtccct  | ggca   | agag     | cattgt   | ggaaa    | atatc    | atca    | actgca   | ttgag   | aagag   | ttaca  | agtcc    | 2160 |
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| gccc    | atcaca | atct     | ctttca   | tga      | aggatct  | aata    | acttaa   | tcct    | catctt  | actg   | gaaccc   | 2280 |
| attcc   | acaga  | acag     | cattcc   | caaca    | agtac    | caca    | agctga   | agg     | ctctcat | gacg   | cagcgg   | 2340 |
| acttat  | ttgc   | agt      | ggccca   | ggag     | aaaagc   | aaac    | gtgggc   | tcttt   | tgggc   | taac   | attaga   | 2400 |
| gccg    | ctttta | atat     | gaaatt   | aac      | actagtc  | actg    | aaaaca   | atgat   | gtgaa   | atct   | taaaaa   | 2460 |
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| cgta    | agtaac | tgt      | ctggagg  | tg       | cctccatt | atc     | ctcatgc  | ctt     | caggaaa | gact   | taacaa   | 2580 |
| aaaca   | atggt  | tc       | atctgggg | aact     | gagcta   | ggc     | ggtgagg  | ttag    | cctgcc  | agtt   | tagagac  | 2640 |

58183US002.ST25.txt

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 Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile  
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 Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val  
 65 70 75 80  
 Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe  
 85 90 95  
 Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu  
 100 105 110  
 Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu  
 115 120 125  
 Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn  
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 Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys  
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 Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro  
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 Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His  
 Page 27

58183US002.ST25.txt  
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58183US002.ST25.txt

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| ctgcattttc tccccagcct catccaattg gatctgtctt tcaattttga acttcaggtc   | 1200 |
| tatcgtgcat ctatgaatct atcacaagca ttttcttcac tgaaaagcct gaaaattctg   | 1260 |
| cggatcagag gatatgtctt taaagagttg aaaagcttta acctctcgcc attacataat   | 1320 |
| cttcaaaatc ttgaagttct tgatcttggc actaacttta taaaaattgc taacctcagc   | 1380 |
| atgtttaaac aatttaaaag actgaaagtc atagatcttt cagtgaataa aatatcacct   | 1440 |
| tcaggagatt caagtgaagt tggcttctgc tcaaatgcc aacttctgt agaaagtat      | 1500 |
| gaacccagg tcttgaaca attacattat ttcagatag ataagtatgc aaggagtgc       | 1560 |
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| cagaccttg atctaagtaa aaatagtata tttttgtca agtcctctga ttttcagcat     | 1680 |
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| aaggttctgc agaaactgat gatgaacgac aatgacatct cttcctccac cagcaggacc   | 1980 |
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| tgggtgggtta accatacggg ggtgactatt cttacctgg ccacagatgt gacttgtgtg   | 2580 |
| gggccaggag cacacaaggg ccaaagtgtg atctccctgg atctgtacac ctgtgagtta   | 2640 |
| gatctgacta acctgattct gttctcactt tccatatctg tatctctctt tctcatggtg   | 2700 |
| atgatgacag caagtcacct ctatttctgg gatgtgtggt atatttacca tttctgtaag   | 2760 |
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| gtgtatgaca ctaaagaccc agctgtgacc gagtgggttt tggctgagct ggtggccaaa   | 2880 |
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58183US002.ST25.txt

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58183US002.ST25.txt

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 Page 33

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 Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu  
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 Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu  
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 930 935 940

58183US002.ST25.txt

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Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln  
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Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu  
 980 985 990

Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys  
 995 1000 1005

Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro  
 1010 1015 1020

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| ctggaaagca agtccttggg agaattagtt ttcagtggca atcgccctga ctttttgtgg   | 1920 |
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| gatttatccc ttaataggct gaagcacatc ccaaataag ctttccttaa ttgcccagcg    | 2040 |
| agtctcactg aactacatat aaatgataat atgttaaagt tttttaactg gacattactc   | 2100 |
| cagcagttcc ctcgtctcga gttgcttgac ttacgtggaa acaaactact ctttttaact   | 2160 |
| gatagcctat ctgactttac atcttccctt cggacactgc tgctgagtca taacaggatt   | 2220 |
| tcccacctac cctctggctt tctttctgaa gtcagtagtc tgaagcacct cgatttaagt   | 2280 |
| tccaatctgc taaaaacaat caacaaatcc gcacttgaaa ctaagaccac caccaaatta   | 2340 |
| tctatgttgg aactacacgg aaaccctttt gaatgcacct gtgacattgg agatttccga   | 2400 |
| agatggatgg atgaacatct gaatgtcaaa attcccagac tggtagatgt cttttgtgcc   | 2460 |
| agtcctgggg atcaaagagg gaagagtatt gtgagtctgg agctgacaac ttgtgtttca   | 2520 |
| gatgtcactg cagtgatatt atttttcttc acgttcttta tcaccaccat ggttatgttg   | 2580 |
| gctgccctgg ctaccattt gttttactgg gatgtttggt ttatatataa tgttgtttta    | 2640 |
| gctaaggtaa aaggctacag gtctctttcc acatcccaaa ctttctatga tgcttacatt   | 2700 |
| tcttatgaca ccaaagatgc ctctgttact gactgggtga taaatgagct gcgctaccac   | 2760 |

58183US002.ST25.txt  
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 cagaggctaa tggatgagaa catggatgtg attatatatta tcctgctgga gccagtgtta 3000  
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<400> 16

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 Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu  
 35 40 45  
 Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr  
 50 55 60  
 Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn  
 65 70 75 80  
 Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His  
 85 90 95  
 Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn  
 100 105 110  
 Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg  
 115 120 125  
 Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu  
 130 135 140

58183US002.ST25.txt

Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn  
 145 150 155 160  
 Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr  
 165 170 175  
 Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile  
 180 185 190  
 Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu  
 195 200 205  
 Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu  
 210 215 220  
 Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu  
 225 230 235 240  
 Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn  
 245 250 255  
 Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly  
 260 265 270  
 Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln  
 275 280 285  
 Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala  
 290 295 300  
 Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe  
 305 310 315 320  
 Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu  
 325 330 335  
 Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser  
 340 345 350  
 Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser  
 355 360 365  
 Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu  
 370 375 380  
 Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn  
 385 390 395 400

58183US002.ST25.txt

Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn  
 405 410 415  
 Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro  
 420 425 430  
 Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln  
 435 440 445  
 Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His  
 450 455 460  
 Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala  
 465 470 475 480  
 Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile  
 485 490 495  
 Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu  
 500 505 510  
 Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala  
 515 520 525  
 Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe  
 530 535 540  
 Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp  
 545 550 555 560  
 Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His  
 565 570 575  
 Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser  
 580 585 590  
 His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys  
 595 600 605  
 Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp  
 610 615 620  
 Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn  
 625 630 635 640  
 Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn  
 Page 39



58183US002.ST25.txt

645                      650                      655

Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn  
                                  660                      665                      670

Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro  
                                  675                      680                      685

Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr  
                                  690                      695                      700

Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser  
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His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser  
                                  725                      730                      735

Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn  
                                  740                      745                      750

Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu  
                                  755                      760                      765

Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg  
                                  770                      775                      780

Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp  
                                  785                      790                      795                      800

Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser  
                                  805                      810                      815

Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe  
                                  820                      825                      830

Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala  
                                  835                      840                      845

His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu  
                                  850                      855                      860

Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr  
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Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp  
                                  885                      890                      895

58183US002.ST25.txt  
Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn  
900 905 910  
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915 920 925  
Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe  
930 935 940  
Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe  
945 950 955 960  
Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile  
965 970 975  
Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu  
980 985 990  
Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro  
995 1000 1005  
Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu  
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Lys Gln Tyr  
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ctggagaagc ccctgcccc cagcatgggt ttctgccga gcgccctgca cccgctgtct 180  
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aacctcaagt ggaactgccc gccggttggc ctgagcccca tgcaactccc ctgccacatg 480  
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## 58183US002.ST25.txt

|  |      |
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| accaacatcc tgatgctaga ctctgccagc ctgcgcggcc tgcattgccct gcgcttccta | 660  |
| ttcatggacg gcaactgtta ttacaagaac ccctgcaggc aggcactgga ggtggccccg  | 720  |
| ggtgccctcc ttggcctggg caacctcacc cacctgtcac tcaagtacaa caacctcact  | 780  |
| gtggtgcccc gcaacctgcc ttccagcctg gagtatctgc tgttgctcta caaccgcatc  | 840  |
| gtcaaaactgg cgctgagga cctggccaat ctgaccgccc tgcgtgtgct cgatgtgggc  | 900  |
| ggaaattgcc gccgctgcga ccacgctccc aacctctgca tggagtggcc tcgtcacttc  | 960  |
| ccccagctac atcccgatac cttcagccac ctgagccgtc ttgaaggcct ggtgttgaaag | 1020 |
| gacagttctc tctcctggct gaatgccagt tggttccgtg ggctgggaaa cctccgagtg  | 1080 |
| ctggacctga gtgagaactt cctctacaaa tgcatacta aaaccaaggc cttccagggc   | 1140 |
| ctaacacagc tgcgcaagct taacctgtcc ttcaattacc aaaagagggt gtcctttgcc  | 1200 |
| cacctgtctc tggccccttc cttcgggagc ctggtcgcgc tgaaggagct ggacatgcac  | 1260 |
| ggcatcttct tccgctcact cgatgagacc acgctccggc cactggcccc cctgccccatg | 1320 |
| ctccagactc tgcgtctgca gatgaacttc atcaaccagg ccagctcgg catcttcagg   | 1380 |
| gccttccttg gcctgcgcta cgtggacctg tcggacaacc gcatcagcgg agcttcggag  | 1440 |
| ctgacagcca ccatggggga ggcagatgga ggggagaagg tctggctgca gcctggggac  | 1500 |
| cttgctccgg cccagtgga cactcccagc tctgaagact tcaggcccaa ctgcagcacc   | 1560 |
| ctcaacttca ccttggtatc gtcacggaac aacctggtga ccgtgcagcc ggagatgttt  | 1620 |
| gcccagctct cgcacctgca gtgcctgctc ctgagccaca actgcatctc gcaggcagtc  | 1680 |
| aatggctccc agttcctgcc gctgaccggc ctgcagggtc tagacctgtc ccgcaataag  | 1740 |
| ctggacctct accacgagca ctcatcacg gagctaccgc gactggaggc cctggacctc   | 1800 |
| agctacaaca gccagccctt tggcatgcag ggcgtgggccc acaacttcag cttcgtggct | 1860 |
| cacctgcgca ccctgcgcca cctcagcctg gcccacaaca acatccacag ccaagtgtcc  | 1920 |
| cagcagctct gcagtacgtc gctgcgggccc ctggacttca gcggcaatgc actgggccat | 1980 |
| atgtgggccc agggagacct ctatctgcac ttcttccaag gcctgagcgg tttgatctgg  | 2040 |
| ctggacttgt cccagaaccg cctgcacacc ctctgcccc aaacctgtcg caacctcccc   | 2100 |
| aagagcctac aggtgctgct tctccgtgac aattacctgg ccttctttaa gtggtggagc  | 2160 |
| ctccacttcc tgcccaaact ggaagtcctc gacctggcag gaaaccggct gaaggccctg  | 2220 |
| accaatggca gcctgcctgc tggcaccggc ctccggaggc tggatgtcag ctgcaacagc  | 2280 |
| atcagcttcg tggcccccg cttcttttcc aaggccaagg agctgcgaga gctcaacctt   | 2340 |
| agcgccaacg ccctcaagac agtggaccac tcctggtttg ggcccctggc gagtgccttg  | 2400 |

## 58183US002.ST25.txt

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 <212> PRT  
 <213> Homo sapiens

<400> 18

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Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe  
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Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu  
 35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn  
 50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp  
 65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp  
 85 90 95

58183US002.ST25.txt

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met  
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 115 120 125  
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 130 135 140  
 Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser  
 145 150 155 160  
 Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly  
 165 170 175  
 Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro  
 180 185 190  
 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr  
 195 200 205  
 Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr  
 210 215 220  
 Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu  
 225 230 235 240  
 Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg  
 245 250 255  
 Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe  
 260 265 270  
 Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly  
 275 280 285  
 Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe  
 290 295 300  
 Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu  
 305 310 315 320  
 Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu  
 325 330 335  
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala  
 340 345 350

## 58183US002.ST25.txt

His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu  
 355 360 365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu  
 370 375 380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met  
 385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly  
 405 410 415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu  
 420 425 430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu  
 435 440 445

Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu  
 450 455 460

Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser  
 465 470 475 480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser  
 485 490 495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val  
 500 505 510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu  
 515 520 525

Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu  
 530 535 540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly  
 545 550 555 560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr  
 565 570 575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser  
 580 585 590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn  
 Page 45

595 58183US002.ST25.txt  
600 605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe  
610 615 620

Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu  
625 630 635 640

His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln  
645 650 655

Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser  
660 665 670

Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg  
675 680 685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg  
690 695 700

Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe  
705 710 715 720

Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala  
725 730 735

Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu  
740 745 750

Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala  
755 760 765

Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu  
770 775 780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser  
785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp  
805 810 815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val  
820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His  
835 840 845

58183US002.ST25.txt

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 850 855 860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln  
 865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu  
 885 890 895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp  
 900 905 910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr  
 915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser  
 930 935 940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu  
 945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg  
 965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val  
 980 985 990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln  
 995 1000 1005

Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg  
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Asn Phe Cys Gln Gly Pro Thr Ala Glu  
 1025 1030

&lt;210&gt; 19

&lt;211&gt; 3002

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 19

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atactattat ttggcagtaa tccagattgc ttttgccacc aacctgaaga catatagagg 180

cagaaggaca ggaataattc tatttgtttc ctgttttgaa acttccatct gtaaggctat 240

caaaaggaga tgtgagagag ggtattgagt ctggcctgac aatgcagttc ttaaaccaaa 300



## 58183US002.ST25.txt

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| acagggtttt gagctcatct tcatcattca tatgaggaaa taagtggtaa aatccttgga  | 480  |
| aatacaatga gactcatcag aaacattttac atattttgta gtattgttat gacagcagag | 540  |
| ggtgatgctc cagagctgcc agaagaaagg gaactgatga ccaactgctc caacatgtct  | 600  |
| ctaagaaagg ttcccgaga cttgaccca gccacaacga cactggattt atcctataac    | 660  |
| ctcctttttc aactccagag ttcagatttt cattctgtct ccaaactgag agttttgatt  | 720  |
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| agatatttag atttgtctaa taacagactg aagagtgtaa cttggtattt actggcaggt  | 840  |
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His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys  
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Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr  
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105

110

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Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr  
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Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys  
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Lys Ser Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu  
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